Design and Implementation of Combinatorial Gradient Libraries

Al Crosby, Paul Smith, Christopher Stafford

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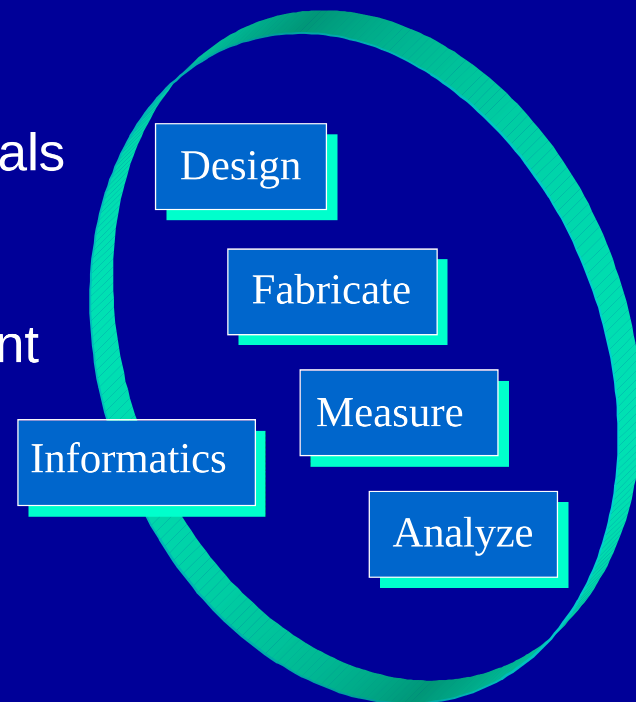
Combinatorial Methods

- What is Combi?
  - A set of tools and techniques which allow a large number of experiments to be conducted in parallel in a short amount of time

- Why Combi?

  Advantages
  - speeds up time for discovery of new materials
  - shortens the time to market
  - lowers material consumption
  - explores parameter space in one experiment

  Challenges
  - requires innovative design of experiment
  - requires some level of automation
  - generates massive amounts of data



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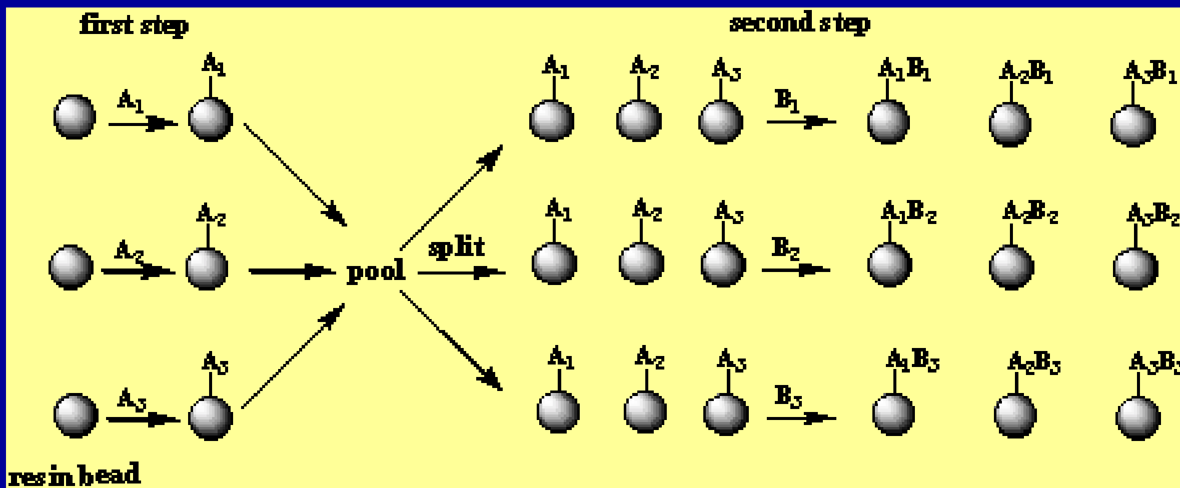

"Split and Pool"

Two popular methods used for pharmaceutical and catalyst discovery.

Microwell Arrays

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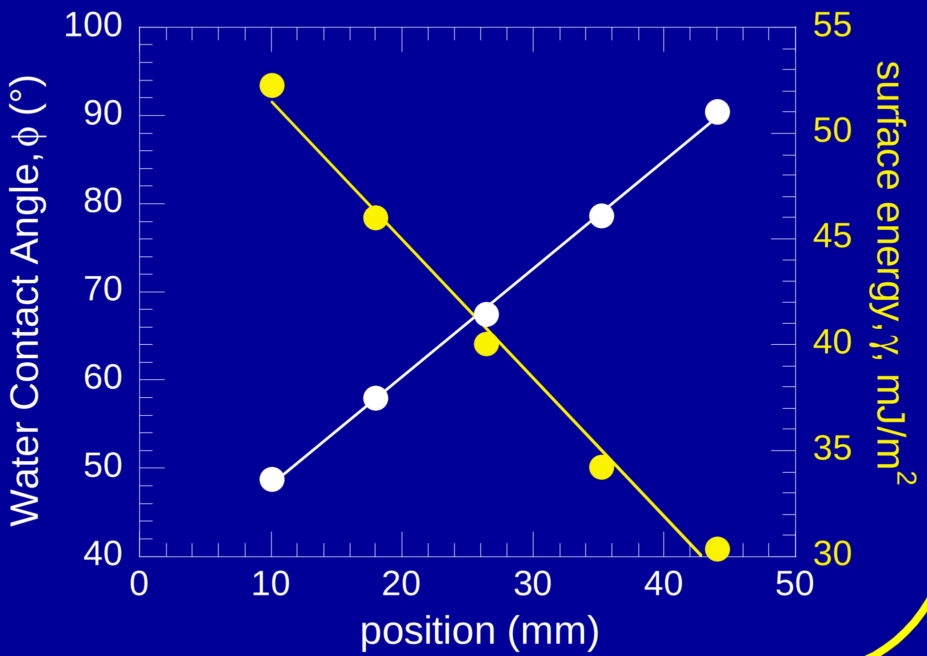
Combinatorial Methods

Gradient Libraries

Library where the experimental parameter changes in a continuous manner as a function of position

Advantages

- No "gaps" in parameter space
- Minimize automation
- Generate "property maps"



Challenges

- Can be hard to create
- Experimental artifacts may be induced
- Difficult to characterize

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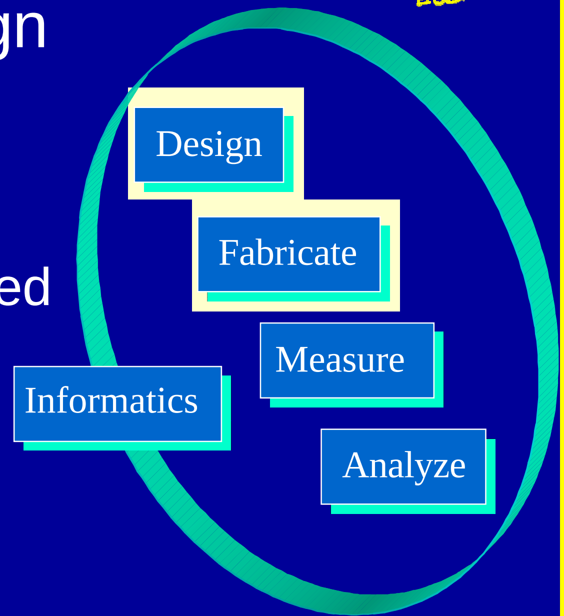
Gradient Library Design and Implementation

Goal: Detail steps for gradient library design

Assumptions:

- Have basic knowledge of problem to be studied
  - Length scale of phenomena
  - Important parameters



- Library characterization is possible

In actual experimental design, all assumptions may not hold. Design process is ITERATIVE in nature.

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Critical Steps for Gradient Library Design

1. Define parameter space
   - What parameters control the problem / process?
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   - What can we learn?
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   - Rational trial and error
   - How do we evaluate success?
4. Refine the method
   - What are the limiting variables?
   - How can we control process variability?
5. Extend the method
   - How far can we stretch our capabilities?

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Define Parameter Space

Problem: Block Copolymer Coatings

Material: PS/PMMA

(cast from dilute solutions)

Critical Variables:

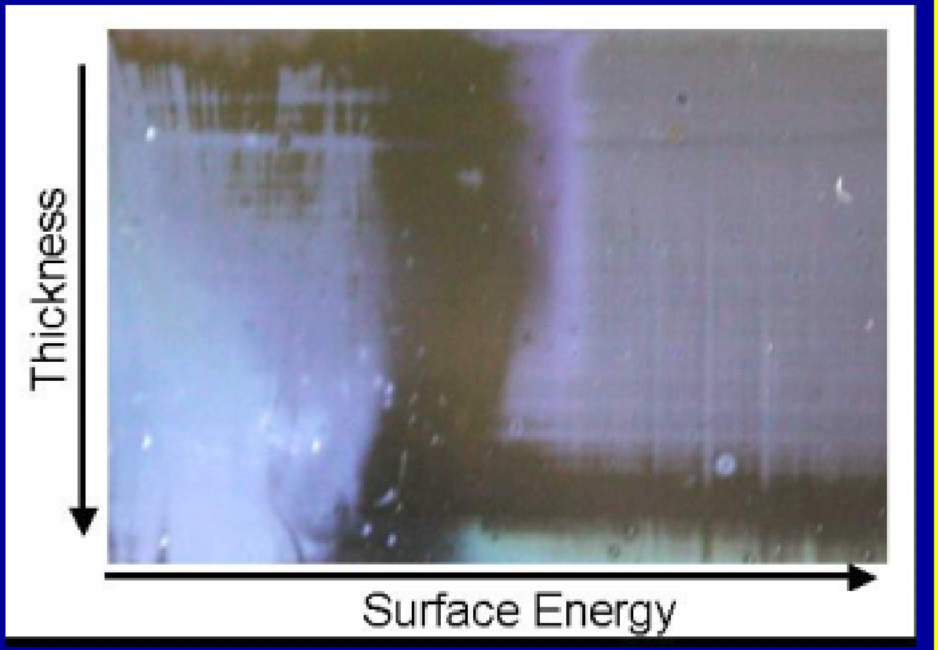
- Temperature
- Film Thickness
- Surface Energy

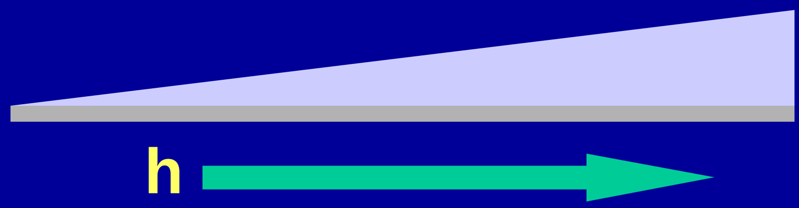
Measurable Parameters:

- Defect/Morphology size

Initial Characterization:

- Optical Microscopy





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Survey Existing Techniques

Begin by surveying existing techniques that might be modified for use in creating the library

For thin film deposition some candidates are:

- Dip Coating
- Doctor Blading
- Meier Rods
- Solvent Casting
- Spin Coating
- Spray Coating

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Survey Existing Techniques

Technique	Thickness Range (m)	Viscosity Range	Reproducibility/ Uniformity
Spin Coating	$10^{-9} – 10^{-5}$	Low-Medium	Excellent
Dip Coating	$10^{-7} – 10^{-3}$	Medium-High	Fair
Spray Coating	$10^{-9} – 10^{-3}$	Low	Fair
Doctor Blade	$10^{-8} – 10^{-3}$	Low-High	Good
Meier Rods	$10^{-6} – 10^{-3}$	Med-High	Good
Solution Cast	$10^{-7} – 10^{-3}$	Low	Poor
Our Needs	$10^{-9} – 10^{-7}$	Low	Good

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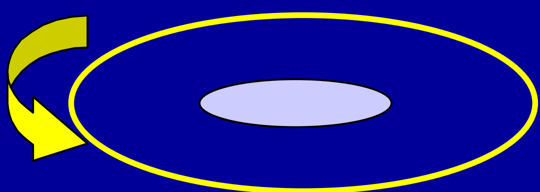
Method Development: Trial 1

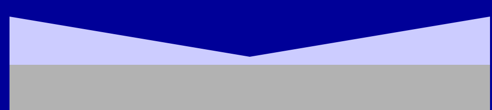
Modification of Spin Coating Technique

- Use low values of acceleration to produce a thickness gradient in the radial direction

Idea

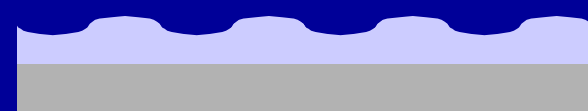


Low acceleration produces a radial gradient in film height



Result

Low acceleration produced non-uniform film, but…



No “gradient” was found

Very hard to control and reproduce

Difficult to characterize film

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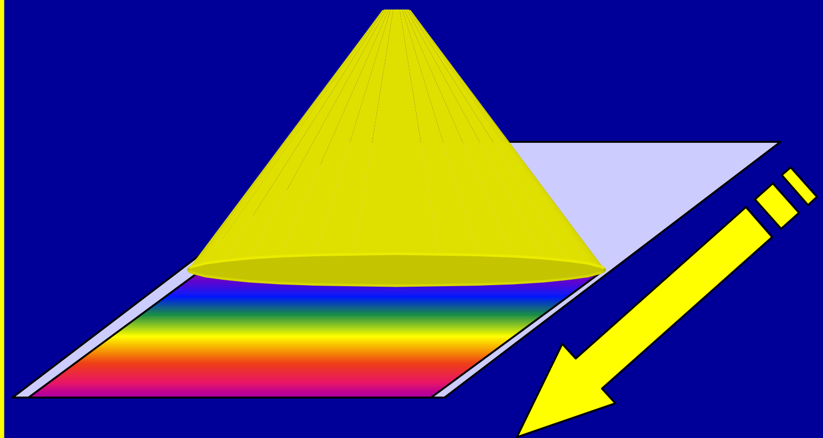
Method Development: Trial 2

Modification of Spray Coating Technique

Spray coat on a substrate moving at variable speed to create a thickness gradient

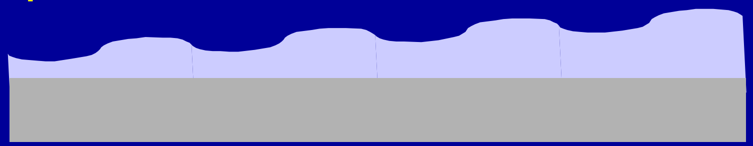
Idea



By changing the stage speed the coating thickness forms a gradient on the substrate

Result

Films with gradually increasing thickness are produced but …



Film thickness non uniform

Thickness of film hard to control

Difficult to characterize film thickness

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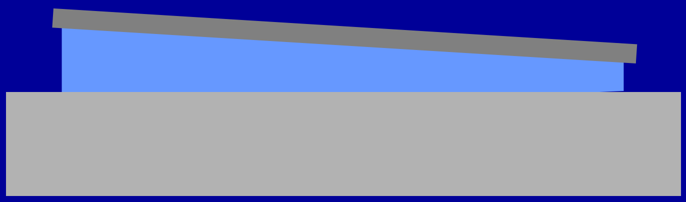
Method Development: Trial 3

Modification of Doctor Blade Technique

Doctor Blade a film on a substrate with a variable blade height to create a thickness gradient

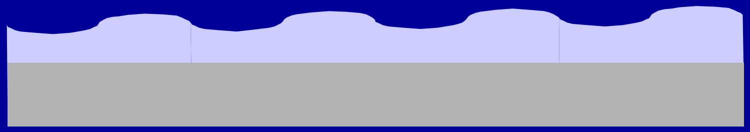
Idea



By varying the blade height across the substrate a gradient in thickness is created

Result

Films had very shallow gradients that were non-uniform and hard to reproduce



However:

It was observed that when the stage speed was changed the “average” film thickness changed

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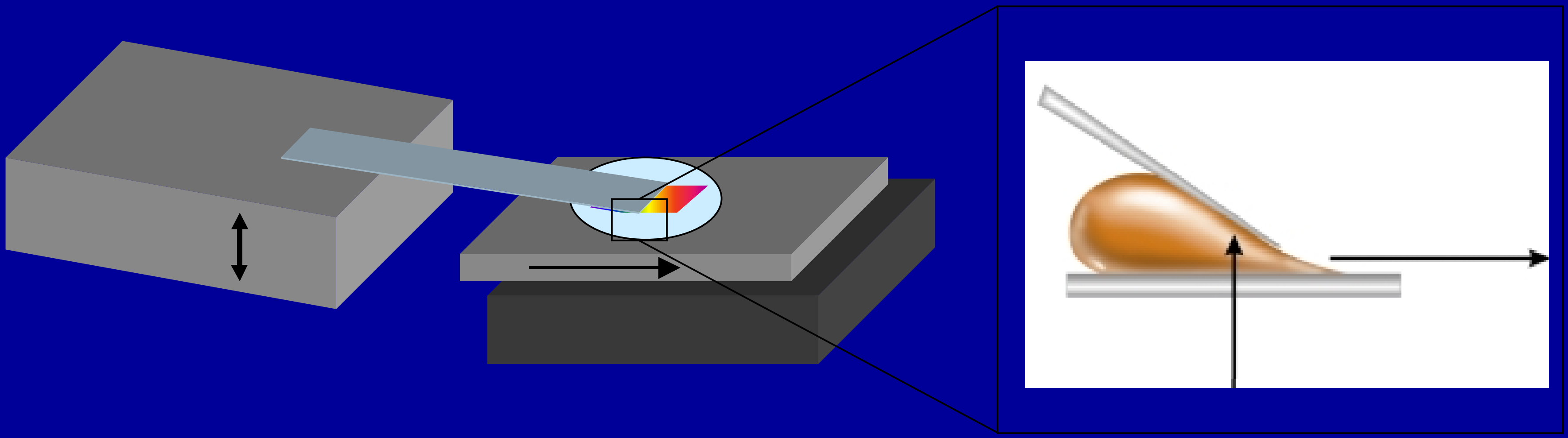
Method Development: Flow Coater

Modification of Doctor Blade Technique

Blade height is kept constant while the substrate accelerates



As the stage velocity increases more of the viscoelastic solution is deposited on the substrate creating a thicker film

Works well for thin films with low viscosity solutions

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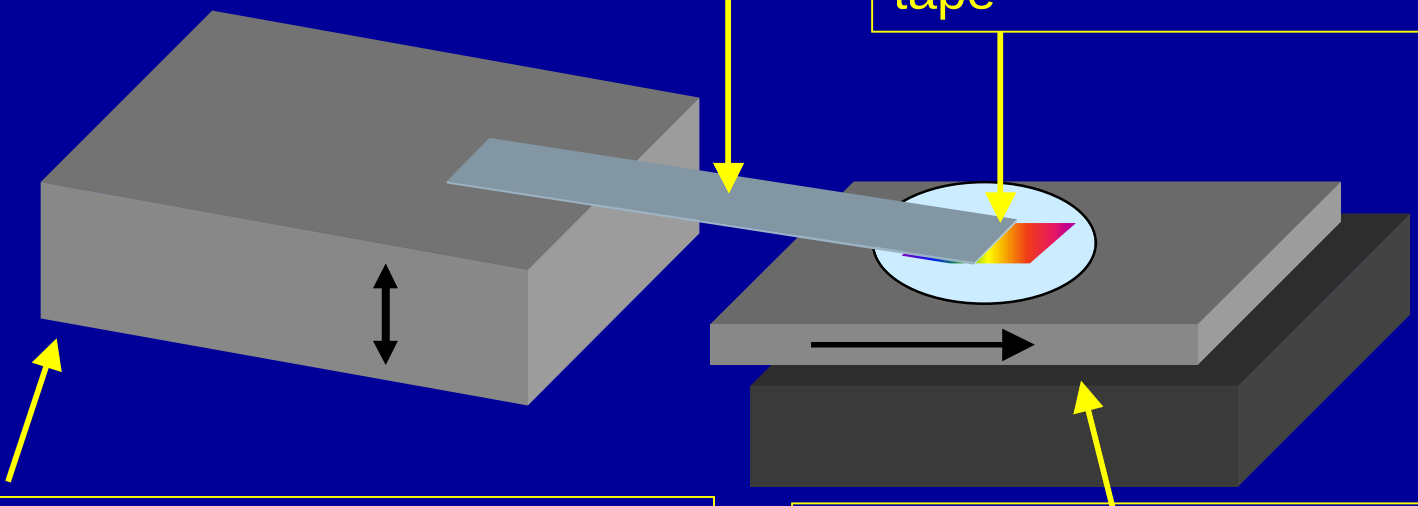
Method Development: Flow Coater

$2 putty knife from Home Depot* with the handle removed

Si Wafer held to stage with tape



Newport* optical mounting stages:
2 “L” brackets
1 height adjustment stage
1 angular adjustment stage

Computer controlled Daedal* motion stage with Parker* Motor ($15,000)
50 mm stage travel
25 mm/sec maximum velocity

* Certain equipment and instruments or materials are identified to adequately specify the experimental details. Such identification does not imply recommendation by NIST.

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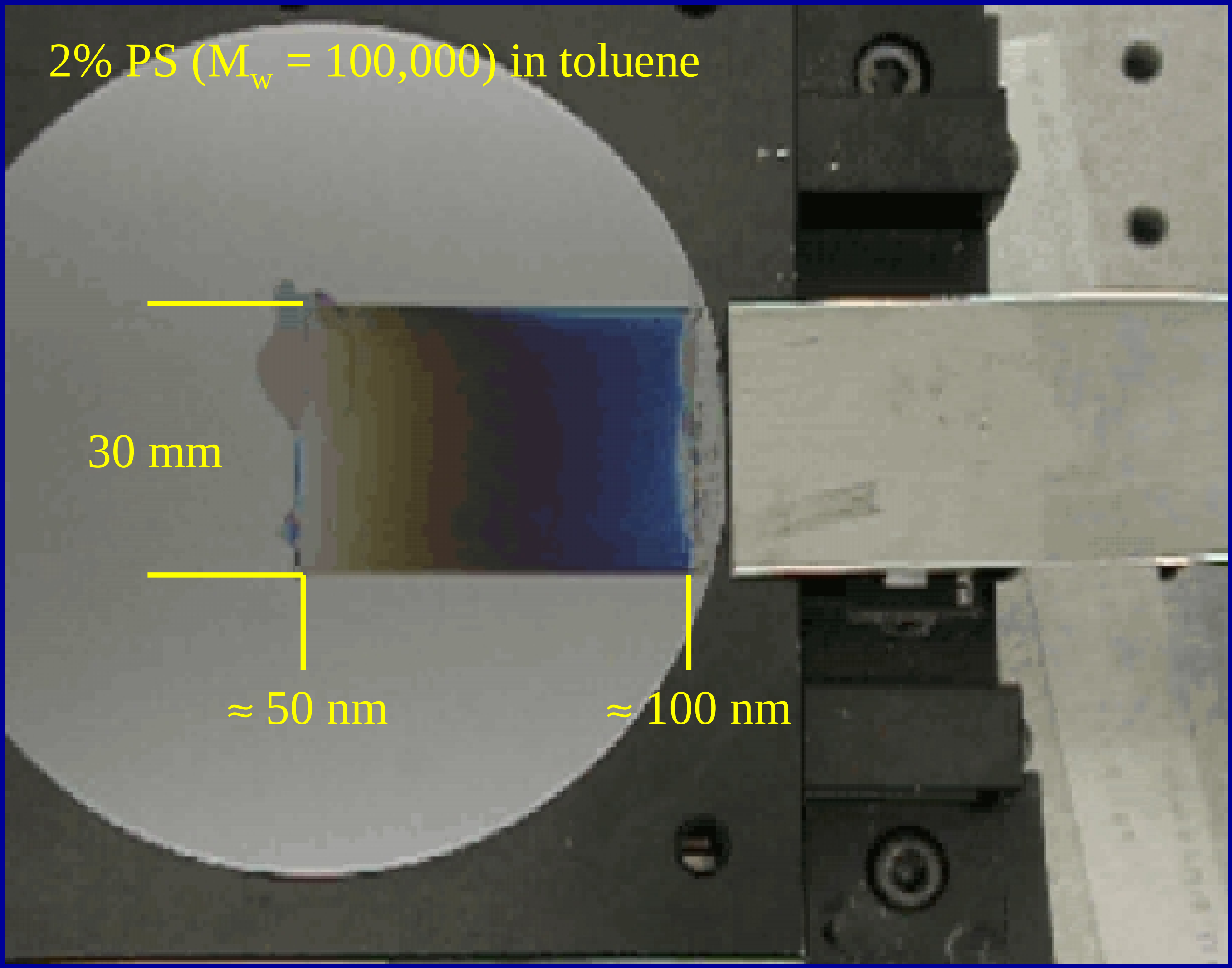
Method Development: Flow Coater



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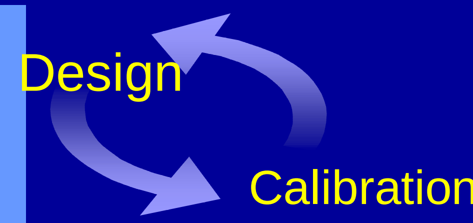

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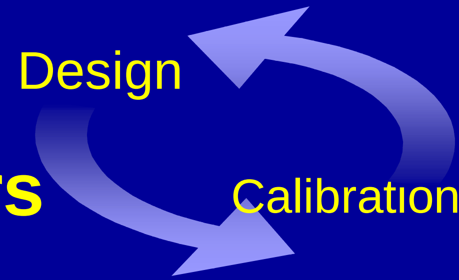
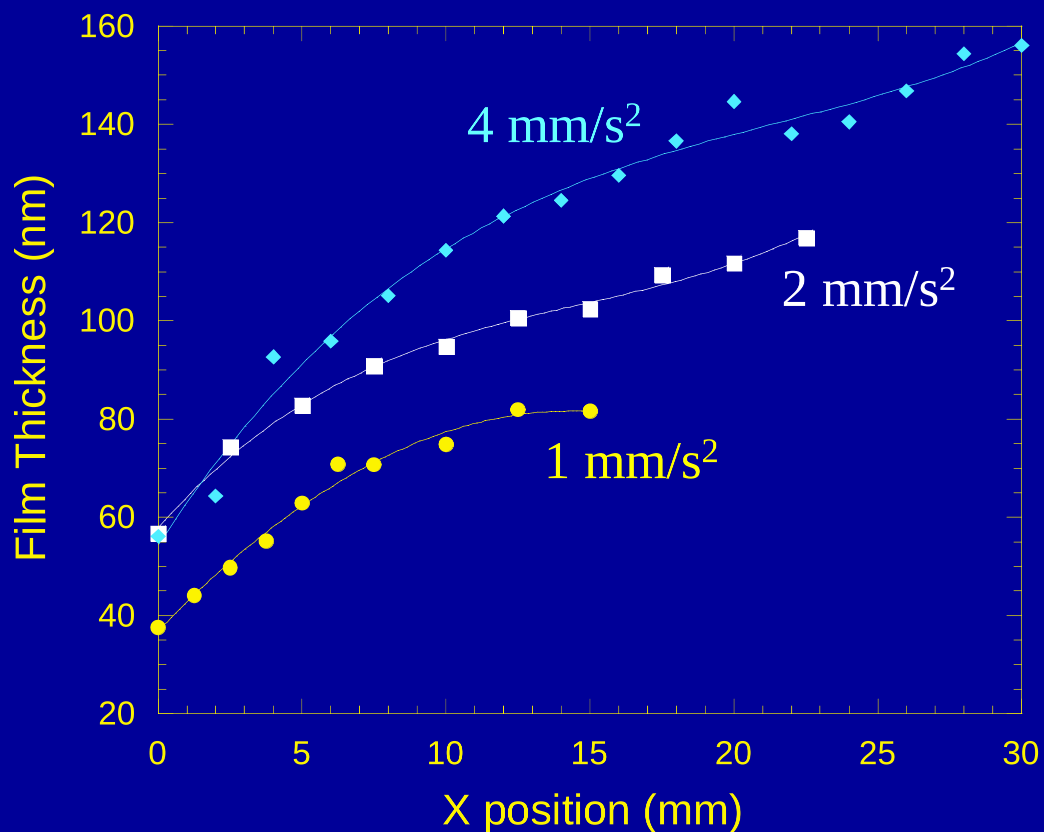
Method Refinement:
Determination of Critical Parameters



Want to determine and understand parameters that influence the library preparation

For the flow coater:
blade height
stage motion parameters
velocity
acceleration
solution viscosity
concentration
polymer M_w



5% PS (M_w = 1800) in toluene

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Extending Capability

Identify the next problem/process:

- Different polymers
- Different solvents
- Different substrates
- Different length scales (i.e. thicker films)

Questions to ask:

- What parameters will change?
- Do we need a new technique?

Examples:

- Casting films at elevated temperatures (incorporate hot plate)
- Casting films from high viscosity solutions (adjust blade height continuously during casting)

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Gradient Library Variables

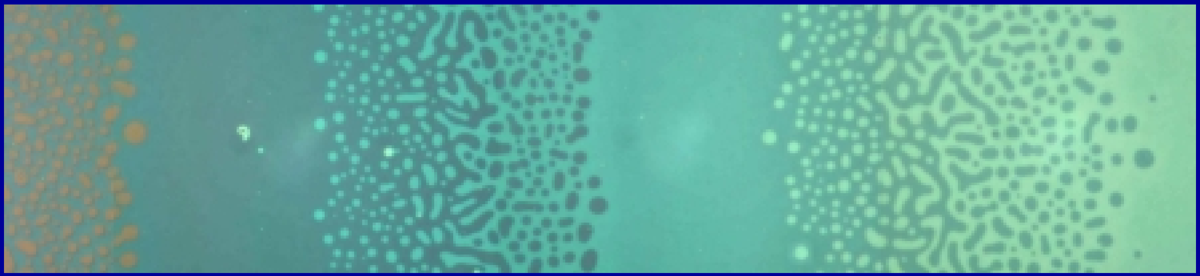
Variables:
- Film thickness
- Crosslink density
- Chemical functionality
- Crystallinity
- Blend composition
- Surface Patterns

Properties:
- Confinement
- Surface energy
- Adhesion energy
- Toughness
- Biocompatibility
- Miscibility / Phase separation
- Wettability

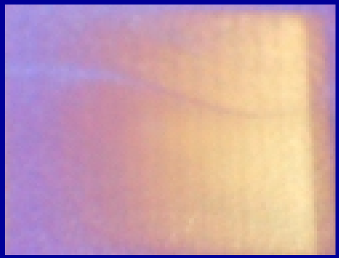
Self-assembled monolayer

UV

Poly(styrene-*b*-methyl methacrylate)
H ~ 70 -120 nm



Poly(vinyl cinnamate)
H ~ 120 nm



UV

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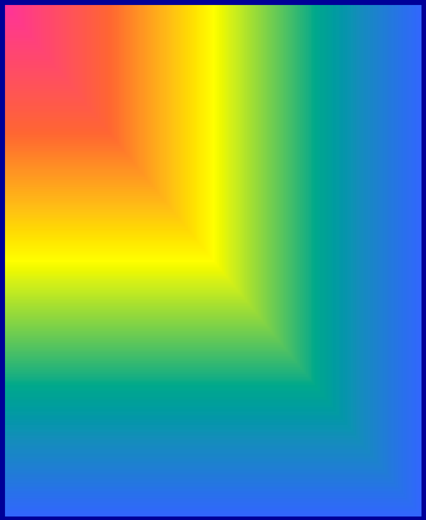
Optimizing Library Efficiency (adding multiple gradients)

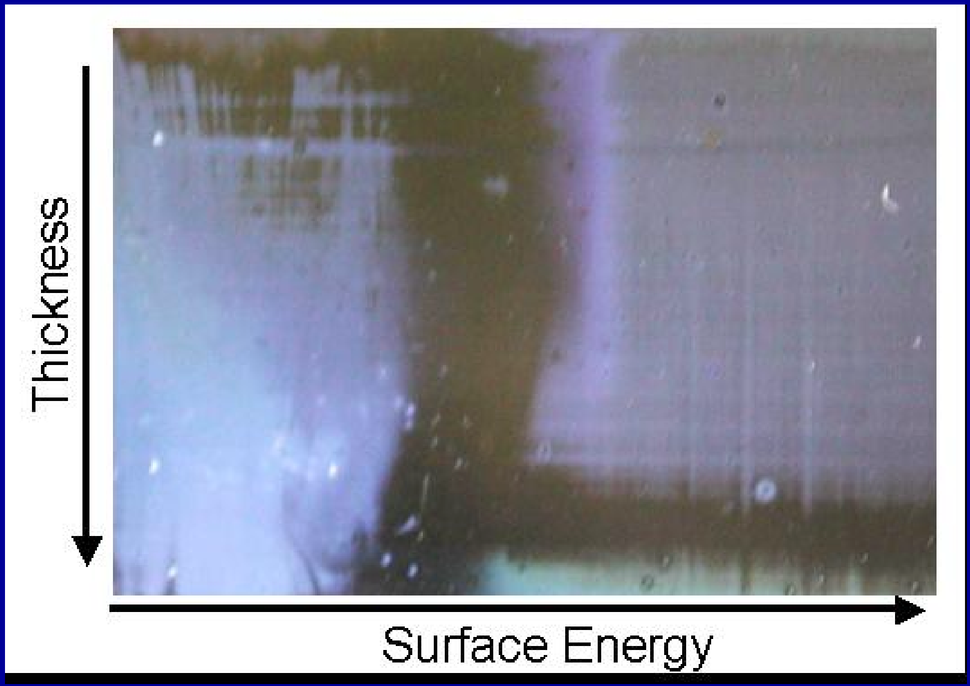
We have only discussed single gradient libraries, but a second dimension remains unused!

Variable 1

Variable 2



For investigating block copolymer coatings, surface energy is a logical second variable



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Critical Issues for Multiple Gradient Libraries

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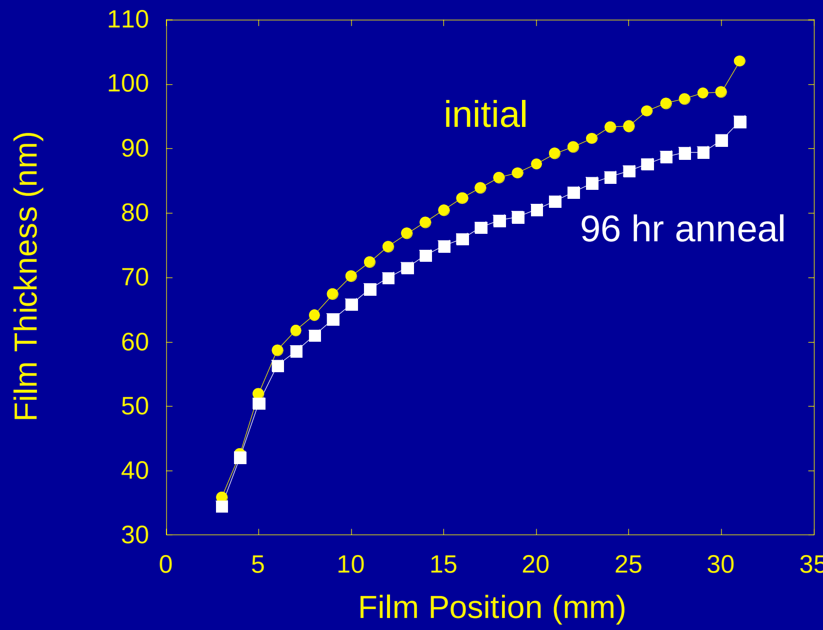
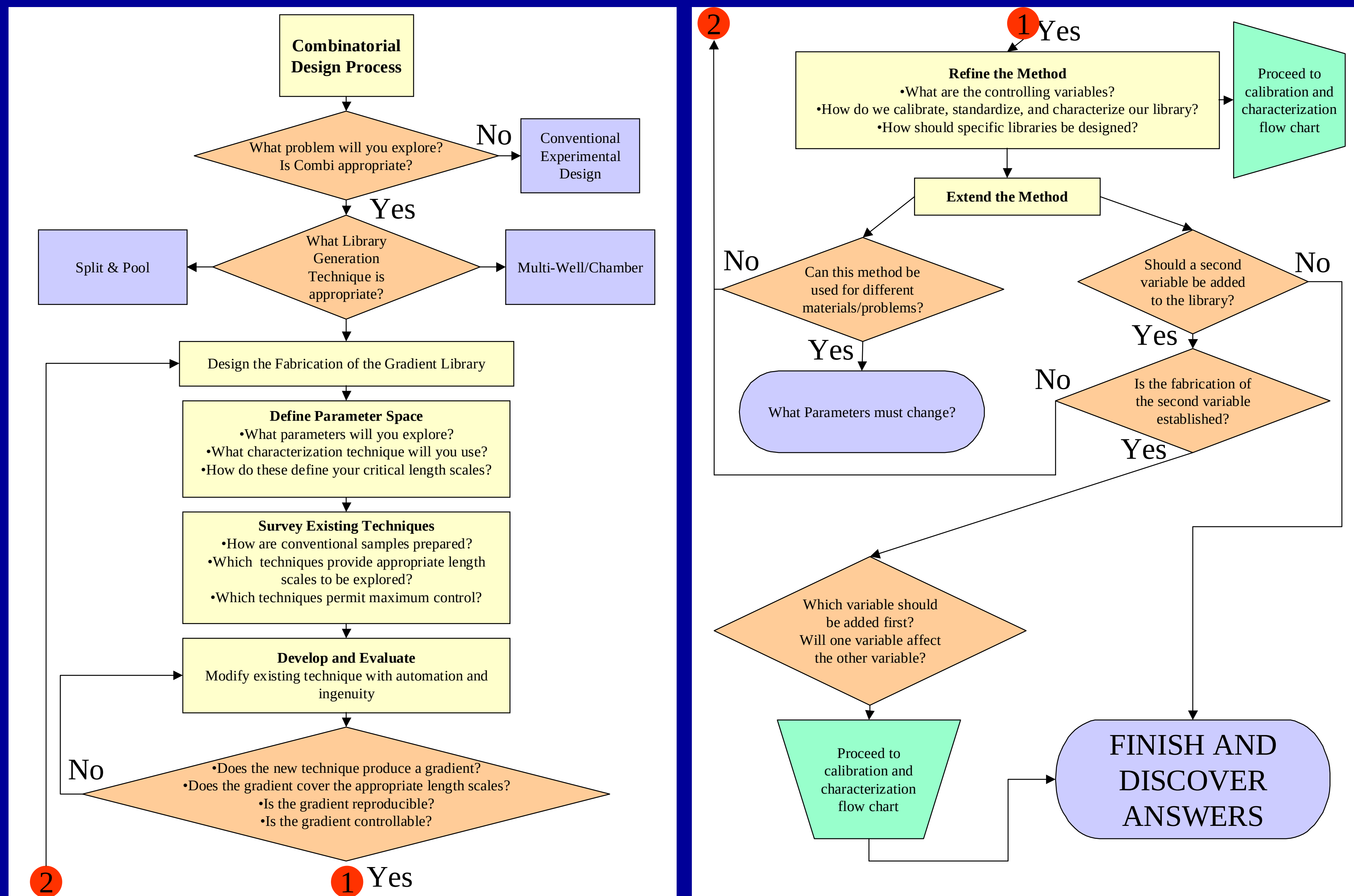
- How will order of preparation influence the library?
- Will one gradient influence the other gradient?
- How stable are the gradients?

Example: Thickness vs. Temperature

- Temperature should be added second
- Temperature can change thickness
- Stability depends upon material and time




Combinatorial Design Process
What problem will you explore? Is Combi appropriate?
No
Conventional Experimental Design
Yes
What Library Generation Technique is appropriate?
Split & Pool
Multi-Well/Chamber
Design the Fabrication of the Gradient Library
Define Parameter Space
•What parameters will you explore?
•What characterization technique will you use?
•How do these define your critical length scales?
Survey Existing Techniques
•How are conventional samples prepared?
•Which techniques provide appropriate length scales to be explored?
•Which techniques permit maximum control?
Develop and Evaluate
Modify existing technique with automation and ingenuity
No
•Does the new technique produce a gradient?
•Does the gradient cover the appropriate length scales?
•Is the gradient reproducible?
•Is the gradient controllable?
2
1 Yes
2
1 Yes
Refine the Method
•What are the controlling variables?
•How do we calibrate, standardize, and characterize our library?
•How should specific libraries be designed?
Proceed to calibration and characterization flow chart
Extend the Method
No
Can this method be used for different materials/problems?
Yes
What Parameters must change?
Should a second variable be added to the library?
No
Yes
No
Is the fabrication of the second variable established?
Yes
Which variable should be added first? Will one variable affect the other variable?
Proceed to calibration and characterization flow chart
FINISH AND DISCOVER ANSWERS